23. (New) A stable, aerosolizable composition that is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject, the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol, about 10-30 parts of water and greater than about 20-80 parts of a glycol selected from the group consisting of polypropylene glycol and polyethylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream.

REMARKS

In the Office Action dated July 9, 2002, claims 1-4 and 7-22 were rejected. Upon entry of this Amendment, claims 1-4, 7-12 and 14-23 are pending and under consideration in the present application. This Amendment shall not be construed as Applicants dedicating any unclaimed or amended subject matter to the public, and Applicants hereby reserve the right to pursue such subject matter in this or related applications.

Applicants respectfully submit that no new matter has been added by way of this Amendment.

Support for new claim 23 can be found at least in now cancelled claim 13.

I. Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1, 9-10 and 12-13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Applicant respectfully disagrees with the Examiner's assertion in view of the amended claims and the remarks presented below. A claim that contains a relative term is "not automatically rendered indefinite under 35 U.S.C.§ 112, second paragraph." M.P.E.P. § 2173.05(b). Moreover, in rejecting a claim under 35 U.S.C. § 112, second paragraph, the Examiner must establish that one of ordinary skill in the pertinent art, when reading the claim in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the specific area set out and circumscribed by the claim. *Ex parte Wu*, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989).

In claim 1 the examiner states the term "stable" is an indefinite term. Applicants submit that stable is a term having definite meaning known by those skilled in the art, nevertheless, the term "stable" is defined in the specification as being a composition that "remains clear through three cycles of freeze/thaw." See page 5, lines 22-27. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner also states that the term "enhanced" in claim 1 is an indefinite term. Applicants submit that enhanced is a term having definite meaning known by those skilled in the art, nevertheless, the specification defines "enhanced" as an increase in the ability of the delta-9-THC to partition from the semiaqueous solution to increase

bioavailability. See page 5, line 32 to page 6, line 3. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner states that the terms "stable" and "rapid" in claim 9 are relative terms that render the claim indefinite. Applicants submit that stable is a term having definite meaning known by those skilled in the art, nevertheless, the term "stable" is defined in the specification as being a composition that "remains clear through three cycles of freeze/thaw." See page 5, lines 22-27. Further, Applicants submit that rapid is a term having definite meaning known by those skilled in the art, nevertheless, the term "rapid" is defined in the specification as crossing the cell membranes of the alveolar epithelial cells, interstituium, and endothelium in less time than aerosolized delt-9-THC in a lipophilic excipient. See page 4, line 26 to page 5, line 21. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner states that the term "suitable liner" in claim 10 is vague and indefinite. Applicants submit that the above amendment to claim 10 cures this defect. Reconsideration and withdrawal of this rejection is respectfully requested in view of the amended claim.

The Examiner states that the claim 12 limitation "wherein the alcohol" lacks an antecedent basis. Applicants submit that the above amendment to claim 12 cures this defect. Reconsideration and withdrawal of this rejection is respectfully requested in view of the amended claim.

The Examiner states that the claim 13 limitation "wherein the glycol" lacks an antecedent basis. Applicants submit that the above amendment to claim 13 cures this

defect. Reconsideration and withdrawal of this rejection is respectfully requested in view of the amended claim.

II. Rejection Under 35 U.S.C. § 103

Claims 1-4 and 7-22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Touitou (5,716,638) in view of Patel *et al.* (6,294,192) in further view of LaMastro *et al.* (5,258,336). The Examiner states "It would have been obvious . . . to teach the composition of Touitou in the form of an aerosol, as taught by Patel et al. because a) Patel et al. and Touitou both teach Compositions comprising THC, ethanol, propylene glycol, and water; b) Patel et al. teach topical, transdermal, and aerosol forms of the composition as possible and interchangeable, and Toutiou teach topical, and transdermal forms of this compositions; hence, the replacement of one pharmaceutical form (topical) of the composition for the other (aerosol) for pharmaceutical purposes would be within the skill one in the art."

The Applicants respectfully disagree and traverse this rejection. Touitou (5,716,638) in view of Patel *et al.* (6,294,192) in further view of LaMastro *et al.* (5,258,336) do not teach or suggest the claimed invention, nor is there any suggestion to one of ordinary skill in the art that there is a reasonable likelihood of success of the present claimed invention.

The burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q. 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable

likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 U.S.P.Q. 2d 1531 (Fed. Cir. 1988). When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U.S.C. § 103. See Ex parte Novitski 26 U.S.P.Q. 2d 1389 (Bd. Pat. App. & Int. 1993) citing In re Clinton, 188 U.S.P.Q. 365 (CCPA 1976).

In view of the amendment and remarks presented herein, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. As taught by the present invention, in one aspect, Applicants claim an aerosolized composition comprising delta-9-tetrahydrocanabinol, ethanol, and propylene glycol. The composition is further defined as having a mean mass median aerodymanic diameter in the range from about 1 up to 10 μM. Moreover, the composition's ratio produces a stable clear solution near the solubility point of the delta-9-tetrahydrocanabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocanabinol from the solvent is enhanced so as to reach the bloodstream.

Applicants use functional language to limit the composition to one suitable for delivery to the lungs so as to allow transfer of the delta-9-tetrahydrocannabinol into the bloodstream. Such a composition is distinct from the topical forms taught by Touitou and the oral forms taught by Patel et al. Functional language in a claim for a composition is a proper limitation. Indeed, MPEP § 2173.05(g) states "[a] functional limitation is often used in association with an element, ingredient or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step."

The Examiner states that the composition would be obvious because Touitou discloses a composition with tetrahydrocannabinol, water, propylene glycol, and ethanol (among other things), Patel *et al.* disclose tetrahydrocannabinol compositions in the form of a spray or an aerosol for pulmonary delivery. The Examiner further noted that "it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose." However, Patel et al. do not teach a pharmaceutical composition suitable for rapid delivery to a lung of a subject and subsequently to the bloodstream; nor does it teach a stable clear solution near the solubility point of delta-9-tetrahydrocannabinol such that the partitioning is enhanced. In fact, Patel et al. use the word pulmonary only once in the specification in a long list of possible dosage forms. Further, Patel et al. do not teach or disclose how to formulate an aerosolized composition suitable for rapid delivery to a lung of a subject. The single reference to an aerosolized composition is for a composition suitable for coating beads for oral delivery, for example, in a capsule, not for delivery to a lung of a subject. *See* Col. 26: ln. 55-60. Patel et al., just as Touitou, do not disclose a composition that is suitable for pulmonary delivery, instead Patel et al. disclose oral dosage forms. See Patel et al. claims (all claims directed to capsules or multiparticulate dosage form). Further, Patel et al. make no reference to the increased partitioning upon delivery as claimed in the present invention. Finally, Patel et al. suggest the mixing of the pharmaceutical composition with water just before administration. Thus, Patel et al. do not teach or suggest a stable aqueous composition. See Patel Col. 26, line 61 to Col. 27, line 10; see also claim 74.

The Examiner further states that it would have been obvious to "teach the composition of the combined references in the type 1 amber glass container of LaMastro et al. because a) the combined references teach a composition in the form aerosol, and a composition that results in aerosolization must be house in a closed container; thus since LaMastro et al. teach their containers for pharmaceutical use and as providing a high degree of chemical stability and protection form ultraviolet light, teaching the container of the combined references as type I amber container would be within the skill of one of one of in the art." However, because claim 9 and 10 also claim the unobvious composition of claim 1 (as detailed above), claims 9 and 10 are also unobvious.

Reconsideration and withdrawal of this rejection is respectfully requested.

III. Unexpected Results

The Examiner states "the data on pages 8-11 of the specification have been considered but not found persuasive because the data merely demonstrates the stability of the instant composition over time." However, Patel et al. suggest the instability of a hydrophobic agent in an aqueous solution. Patel et al. state "Such supersaturated solutions, whether characterized as a clear aqueous dispersions (as initially formed) or as multi-phase solutions (as would be expected if the meta-stable breaks down). . . . Col. 27, line 49-52; see also Col. 26, line 61 to Col. 27, line 10; see also claim 74. Thus, the prior art references actually suggest the non-stability of the compositions and not stability claimed through three freeze/thaw cycles as detailed in the specification.

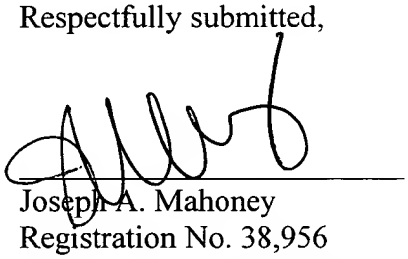
Reconsideration of this evidence is respectfully requested.

CONCLUSION

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-4, 7-12 and 14-23 are in condition for allowance. It is respectfully submitted in view of the foregoing Remarks that all of the objections and rejections in the Office Action dated July 9, 2002 have been overcome and should be withdrawn. Accordingly, reconsideration and withdrawal of the outstanding rejections and allowance of claims 1-4, 7-12 and 14-23 is respectfully solicited. Applicants respectfully request early and favorable notification to that effect.

Respectfully submitted,

Dated: December 9, 2002

By: 

Joseph A. Mahoney
Registration No. 38,956
Mayer, Brown, Rowe & Maw
P.O. Box 2828
190 S. LaSalle Street
Chicago, IL 60690-2828
(312) 701-8979

Version with Markings to Show Changes Made to the Claims

1. (Amended) A stable, aerosolizable composition that is pharmaceutically suitable for rapid bronchial delivery to a lung of a subject, the composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising volumetric ratios of about 10-70 parts of ethanol, about 10-30 parts of water and [>] greater than about 20-80 parts of propylene glycol having a combined total of 100, provided that:

(i) upon aerosolization the composition has a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) the ratio of the ethanol, water and propylene glycol produces a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol such that upon administration to the lung, the partitioning of the delta-9-tetrahydrocannabinol from the solvent is enhanced so as to reach the bloodstream.

3. (Amended) A composition as defined in Claim 2 wherein the amount of delta-9- tetrahydrocannabinol comprises from about 0.1 to 25 mg delta-9-tetrahydrocannabinol/mL of the solvent.

4. (Amended) A composition as defined in Claim 2 wherein the amount of delta-9- tetrahydrocannabinol comprises about 50 mg delta-9-tetrahydrocannabinol/mL of the solvent.

7. (Amended) A composition as defined in Claim 1 wherein the volumetric ratios of ethanol : water : propylene glycol are selected from those in the range of from about 10 – 70 : about 10 : [>] greater than 20 – 80, respectively, having a combined total of 100.

8. (Amended) A composition as defined in Claim 7 wherein the volumetric ratios of ethanol : water : propylene glycol are about 35 : about 10 : about 55, respectively, having a combined total of 100.

10. A sterile and/or preserved sealed unit- or multi-unit dosage form as defined in Claim 9 wherein said container comprises Type I Amber Glass [with a suitable liner].

12. The composition of claim 1, wherein the [alcohol] ethanol is replaced with [is selected from the group consisting of ethanol and] isopropanol.